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EXAMINER

RAO, DEEPAK R

ART UNIT

PAPER NUMBER

1624

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Please find below and/or attached an Office communication concerning this application or proceeding.

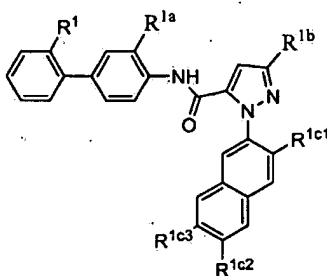
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DETAILED ACTION

Claims 21-23, 25-27, 29-31, 33-35 and 37-39 are pending in this application.

Election/Restrictions

Applicant's election with traverse of the species:



wherein R^1 is selected from the group consisting of: $-S(=O)_2-NH_2$, $-S(=O)_2-Me$, $-CH_2NH_2$, and $-CH_2NMe_2$; R^{1a} is H; R^{1b} is CH_3 or CF_3 ; R^{1c1} is independently selected from the group consisting of: $-H$, $-F$, $-Cl$, $-Br$, $-NH_2$, $-OH$, $-SO_2Me$, $-SO_2Et$, $-SO_2NH_2$, $-NO_2$, $-CN$, $-CONH_2$ and $-CH_2OH$; R^{1c2} is independently selected from the group consisting of: $-H$, $-F$, $-Cl$ and $-Br$; and R^{1c3} is independently selected from the group consisting of: $-H$, $-F$, $-Cl$ and $-Br$

in the reply filed on November 10, 2005 is acknowledged. The traversal is on the ground(s) that the restriction improper because there is no serious search burden.

As the instantly amended claims are drawn to composition and method of use of the compounds, which were previously fully examined and issued in U.S. Patent Nos. 6,632,815 and 6,720,317, the restriction requirement of the previous office action is **withdrawn**, and the pending claims are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23, 25-27, 29-31, 33-35 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for treating venous thrombosis or a method of treating venous thrombosis, does not reasonably provide enablement for a composition for preventing all types of conditions in a mammal characterized by undesired thrombosis; or a method for preventing all types of conditions in a mammal characterized by undesired thrombosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination.

The instant claims recite 'a pharmaceutical composition which is used in the prevention of a condition characterized by undesired thrombosis' and the specification fails to enable one skilled in the art for the recited use. The instant claims appear to be in 'reach-through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions,

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for which they lack written description and enabling disclosure in the specification. Further, there is no disclosure regarding how the patient in need of such activity is identified and further, how an inhibition of factor Xa is generally produced in the patient. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art.

The instant composition claims recite a particular intended use for the composition, i.e., '**preventing** a condition characterized by undesired thrombosis', which according to the specification is directed to a wide list of conditions and the specification, does not provide enablement for all the listed disorders. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claims are drawn to 'a pharmaceutical composition for **preventing** a condition in a mammal characterized by undesired thrombosis' and 'a method for **preventing** a condition in a mammal characterized by undesired thrombosis', which diseases are identified as deep venous thrombosis, pulmonary embolus, etc., see pages 196-197. The scope of the claims includes '**prevention** of all types of conditions characterized by undesired thrombosis' which is not adequately enabled solely based on the biological activity of the compounds provided in the specification.

The instant compounds are disclosed to be inhibitors of factor Xa and are useful as antithrombotic agents and it is recited that the instant compounds are useful in 'treating or

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preventing' several diseases, including stroke, myocardial infarction, etc., for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001, wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (PubMed Abstract) wherein with regards to antithrombotic therapies, it is stated that "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (PubMed Abstract) with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'.

A patient's risk of venous thromboembolism varies depending on multiple factors including age, medical condition, type of surgery, duration of immobilization, and the presence of an underlying hypercoagulable state such as malignancy. Also, the site of cardiogenic thromboembolism is variable. Thromboembolism uncommonly occurs in the setting of a

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structurally normal or mildly abnormal heart. Effective recommendations for prevention of arterial thromboembolism have not been identified. Therefore, primary prevention of thromboembolism is basically a battle against the underlying cardiac disorder. No therapies have been identified that reverse or significantly retard the development of feline heart disease or its related pathologic or prothrombotic sequelae. Moreover, it is likely that multiple interactions are involved in thrombogenesis, including myocardial pathology and cardiac dysfunction, platelets, and other blood components and factors. Furthermore, there is no evidence of record which would enable the skilled artisan in the identification of the subjects that have the potential of needing such 'prevention of the diseases' encompassed by the instant claims. Regarding prevention of stroke, a state of the art reference, Hart et al., states that "Critical issues involving prevention of stroke for millions of persons with atrial fibrillation remain to be resolved by the next generation of studies. Reliable schemes to predict stroke risk must be refined and validated, and optimal antithrombotic prophylaxis awaits better understanding of the mechanisms linking predictors to stroke" (see pages 693-694).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

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1) The nature of the invention: Pharmaceutical composition and a method for **preventing** a condition in a mammal characterized by undesired thrombosis.

2) The state of the prior art: The recent publications of record expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable. The state of the art is not indicative of any anticoagulant agents for inhibiting thrombotic conditions in general. Further there are no known therapeutic or preventative agents for thrombotic conditions generally. Majerus et al. (document enclosed) regarding Primary Prevention of Arterial Thromboembolism states that “the prophylactic use of aspirin in an apparently healthy population is not recommended at this time, unless there are risk factors for cardiovascular disease” (see page 1357). This clearly establishes that many factors need to be evaluated prior to administering anticoagulant or antiplatelet drug therapy in normal individuals. The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive method. **Prevention** is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of thrombotic conditions such as coronary artery diseases, cerebrovascular diseases, etc. never manifest themselves. The state of the art reference, Handin (document enclosed), states that “There are no clinical tests to screen patients suspected of having hypercoagulable or prethrombotic disorders”, thereby indicating the difficulty in identifying the ‘patients in need of’ the preventive treatment. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of the thrombotic conditions of the claims. Venous thromboembolism is often clinically silent.

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As a result, studies evaluating the efficacy of preventive measures generally screen patients who are asymptomatic. As widespread screening is not recommended in general practice, the incidence of venous thromboembolism in most studies appears higher than that encountered in clinical practice. The importance of clinically undetected venous thromboembolism is not fully understood. Also, the diagnosis of pulmonary embolism with or without pulmonary infarction is often difficult to establish unless special procedures are used.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the ‘preventive’ effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.d. 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Regarding the management of thrombotic and cardiovascular disorders using anticoagulants and antithrombotic drugs, a current state of the art reference, Fareed et al., provides that ‘the therapeutic index and efficacy in terms of clinical data of many newly developed drugs is limited and the newer agents must be validated in extended clinical trials’, see the Medline abstract.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Test assays are provided to determine the activity of the compounds in the specification, however, it is not disclosed how these assays and/or results correlate to the instantly claimed **preventive** effect.

6) The breadth of the claims: The instant claims encompass **prevention** of all types of conditions characterized by undesired thrombosis.

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7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards ‘preventing’ the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23, 25-27, 29-31, 33-35 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite “.... effective amount of a compound of formula (I) **and** all pharmaceutically acceptable, salts, thereof”. This is confusing because it is not clear if a compound **or** the salt, etc. is claimed or a mixture of the compound and the salt is claimed. Replacing the term “and” with -- or -- is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23, 25-27, and 33-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Lam et al., WO 98/57951. The instantly claimed composition comprising a compound or method of using the compounds read on the reference disclosed composition and/or method of use taught for the reference disclosed compounds, see the structural formula I in page 5, wherein D is a 6-membered aromatic carbocyclic ring, M is formula t (page 6) and the specific compound of Example 117 in page 182.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-23, 25-27, 29-31, 33-35 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al., WO 98/57951. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula I in page 5 wherein D is a 6-membered aromatic carbocyclic ring; D and E are optionally substituted by R; M is a group of formula t (page 6) wherein Z is -C(O)-NH- (page 8, line 21) and A and B are optionally substituted phenyl. Further, see the exemplified compound Table 1, Ex 117, page 182. The compounds are taught to be useful as factor Xa inhibitors in treating thromboembolic disorders, see the abstract and page 4, lines 27-32.

Claims 21-23, 25-27, and 33-35 read on the teachings of the reference, see the rejection under 35 U.S.C. 102. The remaining claims differs from the reference, by being drawn to a composition or method of use comprising a compound which falls within a subgenus of the reference genus or a species of the reference disclosed generic group of compounds.

Alternatively, the compounds of the claims are positional isomers of the reference compound because they differ by the position of the substituents on the rings, i.e., the compounds of the instant claims differ from the reference disclosed compound 117 by having the fluoro substituent on the phenyl ring at a different position. First, it would have been obvious to one having ordinary skill in the art to select any of the species of the reference, including those instantly claimed. Particularly, it would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare

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the instantly claimed compounds because such species of the reference disclosed genus, including compounds that are isomers of reference disclosed compounds, are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds. It has been held that a compound falling within the prior art genus or which is isomeric with a compound of prior art is *prima facie* obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950). *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Receipt is acknowledged of the Information Disclosure Statement filed on June 20, 2003, and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

January 23, 2006